



Complex Left Atrial Appendage Morphology and Left Atrial Appendage Thrombus Formation in Patients With Atrial Fibrillation

| | |
|----------|---|
| 著者 | 山本 昌良 |
| year | 2015 |
| その他のタイトル | 心房細動患者における左心耳形態と左心耳内血栓との関連性についての検討 |
| 学位授与大学 | 筑波大学 (University of Tsukuba) |
| 学位授与年度 | 2014 |
| 報告番号 | 12102甲第7459号 |
| URL | http://hdl.handle.net/2241/00126792 |

Complex Left Atrial Appendage Morphology and
Left Atrial Appendage Thrombus Formation
in Patients With Atrial Fibrillation

(心房細動患者における左心耳形態と左心耳内血栓
との関連性についての検討)

2 0 1 4

筑波大学大学院博士課程人間総合科学研究科

山本 昌良

Table of Contents

| | |
|---|----|
| Introduction. | 1 |
| Methods. | 2 |
| Study Population and Study Protocol. | 2 |
| Echocardiographic Studies | 3 |
| Quantification of LAA Morphology | 5 |
| Clinical Risk Stratification. | 6 |
| Catheter Ablation | 6 |
| Statistical Analysis | 6 |
| Results. | 7 |
| Risk Factors for LAA Thrombus. | 9 |
| Risk Factors for LAA Thrombus in Patients with Low CHADS ₂ Score | 10 |
| Functional and Morphological Changes After Catheter Ablation | 10 |
| Discussion | 11 |
| Clinical Implications | 14 |
| Study Limitations. | 15 |
| Conclusions | 16 |
| Disclosure. | 16 |
| References. | 17 |
| Table | 23 |
| Figure | 27 |

Introduction

In patients with atrial fibrillation (AF), most thrombus formation occurs in the left atrial appendage (LAA) because the saccate and complex morphology of the LAA induces stasis of blood flow.¹ The CHADS₂ and CHA₂DS₂-VaSc scores are indices of thromboembolic risk for patients with AF.^{2,3} Of the echocardiographic indices, left ventricular systolic dysfunction, dense spontaneous echo contrast (SEC), low LAA peak flow velocities, and complex aortic plaque were reported to be related to thromboembolic risk.⁴⁻⁵ However, whether LAA morphology itself is a risk factor for LAA thrombus formation has not been well studied. Recently, Di Biase et al. assessed the LAA with computed tomography or magnetic resonance imaging and reported the types of morphology related to thromboembolic risk.⁶ That report strongly suggests that LAA morphology is a risk factor for LAA thrombus formation; however, the relation between presence of LAA thrombus and types of LAA morphology has not been clarified. Although computed tomography and magnetic resonance imaging have been used to assess LAA morphology,⁶⁻⁸ initial studies with three-dimensional (3D) transesophageal echocardiography (TEE) have also shown the potential to assess LAA morphology.^{9,10} Recently, our coworkers reported that 3D-TEE could evaluate the LAA volume, orifice area, depth and number of LAA lobes from reconstructed 3D LAA

images.¹¹ Therefore, the aim of our study was to clarify the relation between LAA morphology evaluated with 3D-TEE and LAA thrombus in patients with AF in comparison with conventional indices.

Methods

Study Population and Study Protocol

Between April 2008 and February 2012, 633 consecutive patients who were candidates for catheter ablation for symptomatic drug-resistant AF at the University of Tsukuba Hospital were prospectively enrolled in this study (Table 1). Among them, patients with inadequate TEE imaging quality and severe mitral or aortic valvular diseases and those undergoing hemodialysis or not receiving anticoagulation therapy with warfarin were excluded.

On the day before catheter ablation, transthoracic echocardiography and TEE examinations were performed to identify the presence of LAA thrombus in all patients. Anticoagulation management of warfarin was in accordance with the guideline of The Japanese Circulation Society.¹² In the guideline, the target INR is 2.0 to 3.0 for patients under 70 years and 1.6 to 2.6 for patients 70 years of age or older because an INR of more than 2.6 increases the risk for serious bleeding complications in the Japanese elderly population. All patients received therapeutic anticoagulation therapy at least

over the 3 weeks before TEE.

Sequential TEE examinations were also performed in patients who had maintained sinus rhythm for at least 1 year after catheter ablation to clarify the contribution of AF to left atrium and LAA morphology and function. Ethical approval of the present study was obtained from the local review committee, and all patients provided their written informed consent.

Echocardiographic Studies

Standard two-dimensional transthoracic echocardiographic examinations were performed with an iE33 ultrasound system and S5-2 probe (Philips Medical Systems, Andover, MA). Left ventricular end-diastolic volume, end-systolic volume, and ejection fraction (LVEF) were measured using the modified Simpson's method from the apical view.¹³ The LA volume was measured using the modified Simpson's method from the apical view.¹⁴

TEE was performed with an iE33 ultrasound system and S7-2 probe (Philips Medical Systems). SEC was visually classified into four grades by careful attention to the gain settings adjusted to distinguish background white noise.¹⁵ The severity of SEC was scored as follows: 0: absence of echogenicity, 1+: mild (minimal echogenicity detectable in only a part of the LA cavity with high gain settings), 2+: moderate (denser

swirling during the entire cardiac cycle), and 3+: severe (intense echodensity and very slow swirling patterns in the LAA usually with similar density in the main cavity) as defined in a previous report. Reproducibility of the SEC grade was evaluated between 2 observers in 50 patients selected at random, and the concordance rate was 92% (46/50). Based on the recommendations from the American Society of Echocardiography,¹⁶ blood stasis was quantified by LAA flow velocities, which were measured at approximately 1 cm below the outlet of the LAA cavity using pulsed Doppler. LAA emptying flow velocity was measured in the basal short-axis view from the transverse scan (45° views). The LAA emptying and filling flow velocities were measured as the average of 3 consecutive cardiac cycles in patients with normal sinus rhythm (NSR) and 5 consecutive cardiac cycles in patients with AF. Full-volume mode examinations were performed from 45° views during apnea at end-expiration. To obtain these datasets, 6 sectors were scanned with gating to the electrocardiographic R wave and were automatically integrated into a wide-angle (76×69 degrees) pyramidal data image covering the entire LAA. The frame rate of each image was set at approximately 20 to 30 frames/s. In patients with AF during the examination, zoom mode, which magnified the pyramidal scan by 1 cardiac beat, was used. The frame rate of each image was set at approximately 10 frames/s.

Quantification of LAA Morphology

Quantification of LAA morphology was performed with QLAB GI-3DQ software (Philips Medical Systems). First, multi-reconstruction planes of the LAA were obtained from 3D datasets (pyramidal images) including the LAA at end-systole. The method of determining LAA orifice size is shown in Figure 1A and B.^{17,18} We measured the LAA orifice long and short diameters, orifice area (Figure 1C), and depth of the orifice to a lobe tip (Figure 1B).

The inner border of the LAA was manually traced within the distal area of the orifice, and the transverse images of the longest axis of the LAA trace area were automatically sliced at 10 levels from the orifice to the most distal site. On each sliced transverse image, the inner border was manually traced and reconstructed into a 3D image (Figure 2). On a reconstructed image, we measured LAA volume and the number of LAA lobes, which was assessed based on the definitions by Veinot et al.¹⁹ as follows: “1) LAA lobe was a visible out-pouching from the main tubular body of the LAA, usually demarcated by an external crease; 2) it was internally capable of admitting a 2-mm probe (i.e., it was not simply a tag of external adipose tissue); 3) it was occasionally but not necessarily associated with a change in direction of the main tubular body of the LAA; 4) it could lie in a different anatomic plane than the main tubular body; and 5) by definition, the LAA must have at least 1 lobe.” Intraobserver

and interobserver variability of these parameters was less than 10% in our previous study.¹¹

Clinical Risk Stratification

We calculated CHADS₂ score for clinical risk stratification of stroke in patients with AF.² Some clinical studies have reported a relation between inflammation and AF,²⁰ and C-reactive protein (CRP) is a representative marker of vascular inflammation. B-type natriuretic peptide (BNP) is a marker that increases in patients with structural heart disease, heart failure, and lone AF. It has been reported that the atrium, and not the ventricle, is the main source of BNP in patients with AF,²¹ and BNP is higher in patients with a history of thromboembolism than in patients without this complication.²² Therefore, blood samples to measure plasma high-sensitivity CRP, BNP concentration, and prothrombin time/international normalized ratio (INR) were obtained at the time of TEE examinations.

Catheter Ablation

Three long sheaths were advanced into the LA. Following pulmonary vein angiography, 2 decapolar ring catheters (Lasso, Biosense Webster, Diamond Bar, CA) were placed in the superior and inferior pulmonary veins on one side at a time. An open-irrigation,

3.5-mm-tip deflectable catheter (ThermoCool; Biosense Webster) was used for mapping and ablation. The LA and pulmonary veins were constructed with a 3-dimensional electro-anatomic mapping system (CARTO; Biosense Webster). The ipsilateral pulmonary vein antrum was circumferentially ablated under fluoroscopic, electrogram, and CARTO guidance. Radiofrequency energy was delivered at a power of 20-35 W. The endpoint of ablation was the elimination of all pulmonary vein potentials.

Statistical Analysis

Results are expressed as number (%) or as mean \pm SD. Comparisons between two groups were performed with the Student *t*-test for continuous variables and the Fisher's exact test for categorical variables. One-way analysis of variance (ANOVA) with the post-hoc Tukey-Kramer test was used to compare variables between three or more groups. Multiple logistic analysis was performed to identify independent risk factors for LAA thrombus. A *P* value of <0.05 was considered to indicate statistical significance. These analyses were performed with SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL).

Results

TEE examinations were successfully performed in all patients. We excluded 69 (10.9%)

patients because of inadequate imaging quality for LAA analysis (n=42), not receiving anticoagulation therapy with warfarin (n=12), severe mitral regurgitation (n=8), undergoing hemodialysis (n=5), and severe mitral stenosis (n=2). Finally, this study comprised 564 patients. Among them, LAA thrombus was observed in 36 (6.4%) patients. Comparisons between patients with and without LAA thrombus are summarized in Table 2. Patients with LAA thrombus had a significantly higher prevalence of non-paroxysmal AF ($P<0.001$). Patients with LAA thrombus were significantly older ($P=0.003$) and their LVEF was lower ($P<0.001$) and CHADS₂ score higher ($P<0.001$) than those in patients without LAA thrombus. There was no significant difference in prothrombin time/INR between the 2 groups. In patients with LAA thrombus, plasma high-sensitivity CRP ($P<0.001$) and BNP ($P<0.001$) concentrations were significantly higher than those in patients without LAA thrombus. In patients with LAA thrombus, LAA volume ($P<0.001$) and LA volume ($P<0.001$) were significantly larger with larger LAA orifice area ($P<0.001$) and deeper LAA depth ($P<0.001$) in comparison with those in patients without LAA thrombus. In addition, the number of LAA lobes was significantly higher ($P<0.001$) than that of the patients without LAA thrombus. Degree of SEC was significantly higher ($P<0.001$) with lower LAA emptying velocities ($P<0.001$) compared with those in patients without LAA thrombus.

Risk Factors for LAA Thrombus

Various factors had a significant relation with the presence of LAA thrombus as shown in Table 3. In a multivariate logistic analysis, number of LAA lobes (OR 2.469, 95% CI 1.495-4.078, $P<0.001$) was identified as an independent risk factor for presence of LAA thrombus, as were CHADS₂ score (OR 1.752, 95% CI 1.237-2.483, $P=0.002$), LVEF (OR 0.962, 95% CI 0.934-0.992, $P=0.01$), LA volume (OR 1.018, 95% CI 1.003-1.032, $P=0.02$), and degree of SEC (OR 1.783, 95% CI 1.102-2.740, $P=0.02$). Prevalence of the number of LAA lobes is shown in Figure 3. The majority of patients with LAA thrombus (32/34, 94.4%) had 3 or more LAA lobes. In contrast, LAA thrombus was observed in only 2 (0.7%) of 296 patients with 1 or 2 lobes. In a multiple logistic regression analysis model, as compared with an LAA with 1 or 2 lobes, an LAA with 3 lobes was 8.6 times (OR 8.6, 95% CI 1.9-39.8, $P=0.006$), 4 or 5 lobes was 10 times (OR 10.0, 95% CI 2.2-42.1, $P=0.004$), and 3 or more lobes was 9.2 times (OR 9.2, 95% CI 2.0-41.1, $P=0.004$) more likely to have thrombus.

The relation of number of LAA lobes with degree of SEC and LAA emptying velocity is shown in Figure 4. In patients with 3 or more LAA lobes, a higher degree of SEC (Figure 4A) and lower LAA emptying velocity (Figure 4B) were observed as compared with those in patients with 1 or 2 LAA lobes.

Risk Factors for LAA Thrombus in Patients with Low CHADS₂ Score

Patients with LAA thrombus included 13 (13/198, 6.6%) with a CHADS₂ score of 1 and 1 (1/185, 0.5%) patient with a CHADS₂ score of 0. In a multiple logistic regression analysis model for LA thrombus in only limited patients with CHADS₂ score 0/1, number of LAA lobes (OR 2.8, 95% CI 1.3-6.1, $P=0.008$) was identified as a significant predictor as were SEC (OR 3.1, 95% CI 1.5-6.6, $P=0.003$) and LVEF (OR 0.9, 95% CI 0.89-0.98, $P=0.022$). Unlike the analysis in the overall population, LA volume was not a significant predictor.

Functional and Morphological Changes After Catheter Ablation

Repeat TEE examinations were performed in 46 patients who maintained sinus rhythm over 1 year after catheter ablation. Average term from catheter ablation to next TEE examination was 19.2 ± 5.3 months. A representative case is shown in Figure 5. The LAA volume decreased after catheter ablation from 17.8 ml to 10.3 ml, while number of lobes and fundamental morphology was maintained. Comparison of clinical characteristics and echocardiographic measurements between baseline and after catheter ablation are summarized in Table 4. After catheter ablation, plasma high-sensitivity CRP ($P=0.04$) and BNP ($P<0.001$) concentrations were decreased, and LVEF

($P=0.002$) was increased. In addition, significant reverse remodeling of both the left atrium ($P<0.001$) and LAA ($P<0.001$) were observed with improvements of blood stasis represented as SEC ($P<0.001$) and LAA emptying velocity ($P=0.02$). However, the number of lobes did not change in any of the patients.

Discussion

This is the first study, to our knowledge, to examine the relation between LAA morphology assessed by 3D-TEE and LAA thrombus formation in patients with AF. We found a significant relation between LAA morphology and the prevalence of LAA thrombus formation; in particular, number of LAA lobes was identified as an independent risk factor for LAA thrombus. The LAA with multiple lobes is thought to have a more complex morphology. Therefore, we believe that complex LAA morphology should be considered as a novel risk factor for the formation of LAA thrombus in patients with AF, as well as CHADS₂ score, LA volume, LVEF, and degree of SEC, which are other well-known risk factors of LAA thrombus.

In patients who maintained sinus rhythm during the first year after catheter ablation, LA and LAA volumes were decreased, but number of LAA lobes did not change. This finding indicates that the number of LAA lobes is a congenital characteristic and is not influenced by LAA remodeling. Accordingly, the complexity of the LAA, which is

represented by the number of LAA lobes, may be a congenital and specific factor in each individual. Several prior studies have reported on the diversity of LAA lobes and their geometry.^{6-10,19,23} In a large autopsy series comprising 500 normal human hearts (age range 0 to 100 years), the distribution of the number of LAA lobes was 2 (54% of hearts), 3 (23%), 1 (20%), and 4 (3%).¹⁹ In our study, the distribution was 2 (42.2%), 3 (34.9%), 1 (10.3%), 4 (11.3%), and 5 (1.2%). Mean number of LAA lobes is 2.1 in the autopsy study and 2.5 in our study, and there was a statistically significant difference by chi-square test ($P<0.01$). The difference might be caused by study populations, namely, our study consisted of patients with AF, in contrast to the normal hearts in the autopsy study.

Di Biase et al. categorized LAA into four different morphologies and reported that the Chicken Wing LAA morphology was less likely to produce an embolic event.⁶ We did not analyze morphology type in the present study; however, morphology such as the Chicken Wing type is the simplest among the Di Biase et al. classification and may correspond to the LAA with 1 or 2 lobes in our study. Di Biase et al. did not discuss the reason why simple LAA morphology was related to a lower embolic event rate. As it is assumed that a simple morphology is less likely to induce blood stasis, the present study clearly revealed that an increase in the number of LAA lobes was related to a high degree of SEC and low LAA emptying velocity. The findings suggest that complex LAA

morphology characterized by an increased number of lobes is likely to induce blood stasis, which is a fundamental cause of thrombus formation.

CT and MRI are useful methods of characterizing the LAA; however, image quality is severely deteriorated by stitching artifact in patients with AF during the examination. We used zoom mode, which magnified the pyramidal scan by 1 cardiac beat in patients with AF during the examination, so we could avoid stitching artifact. Moreover, CT has a problem of radiation exposure and both methods require use of a contrast agent, so it is difficult to use in patients with severe renal dysfunction. In most hospitals, TEE was generally performed before catheter ablation for AF to assess LAA thrombus. TEE has the advantage of assessing LAA morphology in routine clinical practice.

Because we managed anticoagulation based on the guideline of the Japanese Circulation Society, the target ranges differ slightly from those in the AHA guidelines or those of other western countries. The Japanese Circulation Society guideline recommends a basic target INR of 2.0 to 3.0. However, in patients 70 years of age or older, the recommended target INR is 1.6 to 2.6 because an INR of more than 2.6 increases the risk for serious bleeding complications in the Japanese elderly population. In our patients without thrombus, 482 (482/528, 91.3%) achieved the target INR, and in patients with thrombus, 33 (33/36, 91.7%) achieved the target INR. In the 3 patients with thrombus who did not achieve the target INR, thrombus formation might be due to

poor warfarin control. However, the INR in these 3 patients was not much lower than the target INR (every patient exceeded an INR of 1.5) because they were all older than 70 years of age. Therefore, most patients with thrombus were treated within the target INR.

Plasma CRP concentrations in patients with LAA thrombus were increased over those in patients without LAA thrombus. Previous studies reported that CRP and interleukin-6 were elevated in patients with AF, and elevated inflammatory markers are related to embolic events.^{24,25} Our findings support these results, but multivariate analysis could not identify the independent strength of the association of these variables with LAA thrombus as compared with that of LAA morphology and blood stasis. Because a significant relation between inflammation and LA remodeling has been observed, the inflammation process may indirectly contribute to LAA thrombus formation via LA and/or LAA remodeling.

Clinical Implications

In this study, we clarified the relation between LAA morphology and thrombus formation. In the clinical setting, we have used the CHADS₂ or CHA₂DS₂-VaSc score for thromboembolic risk stratification. However, in cases of high bleeding risk or low CHADS₂ score (0 or 1), both bleeding risk due to anticoagulation therapy and

thromboembolic risk should be considered. Furthermore, in patients who have maintained sinus rhythm for a long time after catheter ablation, we wonder whether anticoagulation therapy should be continued. Knowledge of the number of LAA lobes would be helpful in making clinical decisions on antithrombotic therapy in such controversial cases. However, thrombus is a cause of stroke, and thrombus formation is no more than a surrogate for stroke risk. In the future, long-term follow-up studies identifying how the number of LAA lobes together with the CHADS₂ score influences the risk of stroke as an end-point are needed.

Study Limitations

Forty-two patients (6.6%), most of whom were in an AF rhythm at the time of TEE examination, were excluded because of inadequate 3D LAA image quality. Because the full-volume imaging method derived from 6 cardiac beats was not available in patients with AF, the single-beat image acquisition method (zoom-mode imaging) was used, which may exacerbate image quality in assessing LAA morphology in patients with AF. From the statistical aspect, there is a great difference between the number of patients with thrombus (n=528) and without thrombus (n=36). Therefore, comparisons between two groups are limited statistically. Furthermore, our study was a single-center study, and the study population was limited to patients undergoing catheter ablation and

anticoagulation therapy with warfarin for AF. To confirm whether this study is applicable to a wider population not undergoing catheter ablation or taking warfarin, a multicenter study consisting of a larger number of participants with diverse diagnoses is necessary.

Conclusions

Complex LAA morphology that was characterized by an increased number of LAA lobes was associated with the presence of LAA thrombus, independently of clinical risk and blood stasis. Our study suggested that LAA morphology might be a congenital risk factor for LAA thrombus formation in patients with AF. Accordingly, analysis of LAA morphology may provide additional information in the diagnosis of LAA thrombus and in decision making and formulation of medical strategies including anticoagulation management.

Disclosures

None.

References

1. Mugge A, Kuhn H, Nikutta P, Grote J, Lopez JA, Daniel WG. Assessment of left atrial appendage function by biplane transesophageal echocardiography in patients with nonrheumatic atrial fibrillation: Identification of a subgroup of patients at increased embolic risk. *J Am Coll Cardiol*. 1994;23:599–607.
2. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC, Jr., Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/GBPA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257–354.
3. European Heart Rhythm Association, European Association for Cardio-Thoracic

Surgery, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–2429.

4. Zabalgaitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke prevention in atrial fibrillation iii investigators. *J Am Coll Cardiol*. 1998;31:1622–1626.
5. Atrial Fibrillation Investigators. Echocardiographic predictors of stroke in patients with atrial fibrillation: A prospective study of 1066 patients from 3 clinical trials. *Arch Intern Med*. 1998;158:1316–1320.
6. Di Biase L, Santangeli P, Anselmino M, Mohanty P, Salvetti I, Gili S, Horton R, Sanchez JE, Bai R, Mohanty S, Pump A, Cereceda Brantes M, Gallinhouse GJ, Burkhardt JD, Cesarani F, Scaglione M, Natale A, Gaita F. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol*.

2012;60:531–538.

7. Lacomis JM, Goitein O, Deible C, Moran PL, Mamone G, Madan S, Schwartzman D. Dynamic multidimensional imaging of the human left atrial appendage. *Europace*. 2007;9:1134–1140.
8. Heist EK, Refaat M, Danik SB, Holmvang G, Ruskin JN, Mansour M. Analysis of the left atrial appendage by magnetic resonance angiography in patients with atrial fibrillation. *Heart Rhythm*. 2006;3:1313–1318.
9. ShGBP SJ, Bardo DM, Sugeng L, Weinert L, Lodato JA, Knight BP, Lopez JJ, Lang RM. Real-time three-dimensional transesophageal echocardiography of the left atrial appendage: Initial experience in the clinical setting. *J Am Soc Echocardiogr*. 2008;21:1362–1368.
10. Agoston I, Xie T, Tiller FL, RGBPman AM, GBPmad M. Assessment of left atrial appendage by live three-dimensional echocardiography: Early experience and comparison with transesophageal echocardiography. *Echocardiography*. 2006;23:127–132.
11. Nakajima H, Seo Y, Ishizu T, Yamamoto M, Machino T, Harimura Y, Kawamura R, Sekiguchi Y, Tada H, Aonuma K. Analysis of the left atrial appendage by three-dimensional transesophageal echocardiography. *Am J Cardiol*. 2010;106:885–892

12. JCS Joint Working Group. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): digest version. *Circ J*. 2010;74:2479–2500.
13. Nosir YF, Vletter WB, Boersma E, Frowijn R, Ten Cate FJ, Fioretti PM, Roelandt JR. The apical long-axis rather than the two-chamber view should be used in combination with the four-chamber view for accurate assessment of left ventricular volumes and function. *Eur Heart J*. 1997;18:1175–1185.
14. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
15. Vincelj J, Sokol I, Jaksic O. Prevalence and clinical significance of left atrial spontaneous echo contrast detected by transesophageal echocardiography. *Echocardiography*. 2002;19:319–324.

16. Transesophageal echocardiography in atrial fibrillation: Standards for acquisition and interpretation and assessment of interobserver variability. Stroke Prevention in Atrial Fibrillation Investigators Committee on Echocardiography. *J Am Soc Echocardiogr.* 1996;9:556–566.
17. Cabrera JA, Ho SY, Climent V, Sanchez-Quintana D. The architecture of the left lateral atrial wall: a particular anatomic region with implications for ablation of atrial fibrillation. *Eur Heart J.* 2008;29:356–362.
18. Budge LP, Shaffer KM, Moorman JR, Lake DE, Ferguson JD, Mangrum JM. Analysis of in vivo left atrial appendage morphology in patients with atrial fibrillation: A direct comparison of transesophageal echocardiography, planar cardiac CT, and segmented three-dimensional cardiac CT. *J Interv Card Electrophysiol.* 2008;23:87–93.
19. Veinot JP, Harrity PJ, Gentile F, Khandheria BK, Bailey KR, Eickholt JT, Seward JB, Tajik AJ, Edwards WD. Anatomy of the normal left atrial appendage: a quantitative study of age-related changes in 500 autopsy hearts: implications for echocardiographic examination. *Circulation.* 1997;96:3112–3115.
20. Boos CJ, Anderson RA, Lip GY. Is atrial fibrillation an inflammatory disorder? *Eur Heart J.* 2006;27:136–149.

21. Inoue S, Murakami Y, Sano K, Katoh H, Shimada T. Atrium as a source of brain natriuretic polypeptide in patients with atrial fibrillation. *J Card Fail.* 2000;6:92–96.
22. Shimizu H. High plasma brain natriuretic polypeptide level as a marker of risk for thromboembolism in patients with nonvalvular atrial fibrillation. *Stroke.* 2002;33:1005–1010.
23. Agmon Y, Khandheria BK, Gentile F, Seward JB. Echocardiographic assessment of the left atrial appendage. *J Am Coll Cardiol.* 1999;34:1867–1877.
24. Psychari SN, Apostolou TS, Sinos L, Hamodraka E, Liakos G, Kremastinos DT. Relation of elevated c-reactive protein and interleukin-6 levels to left atrial size and duration of episodes in patients with atrial fibrillation. *Am J Cardiol.* 2005;95:764–767.
25. Conway DS, Buggins P, Hughes E, Lip GY. Prognostic significance of raised plasma levels of interleukin-6 and C-reactive protein in atrial fibrillation. *Am Heart J.* 2004;148:462–466.

Table 1 Baseline Characteristics and Echocardiographic Measurements

| Variable | Value (N=633) |
|---|----------------------|
| Men/Women | 512/121 |
| Age (years) | 62 ± 11 |
| Heart rate | 67 ± 16 |
| Co-morbidities | |
| Paroxysmal atrial fibrillation | 373 (59%) |
| Non-paroxysmal atrial fibrillation | 260 (41%) |
| Rhythm at examination | |
| Normal sinus rhythm | 365 (58%) |
| Atrial fibrillation | 268 (42%) |
| Measurements on 2D transthoracic echocardiography | |
| Left ventricular end-diastolic volume (ml) | 101 ± 36 |
| Left ventricular end-systolic volume (ml) | 38 ± 26 |
| Left ventricular ejection fraction (%) | 63 ± 11 |
| Left atrial volume (ml) | 63 ± 29 |

Data are expressed as mean ± SD or as number (percentage).

Table 2 Baseline Characteristics According to Presence of LAA Thrombus

| Variable | No thrombus (n = 528) | Thrombus (n = 36) | p Value |
|--|--------------------------|----------------------|---------|
| Age (years) | 61 ± 11 | 67 ± 8 | 0.003 |
| AF type (Non-paroxysmal AF) | 186 (35%) | 26 (72%) | 0.0001 |
| Sex (male) | 424 (80%) | 33 (92%) | ns |
| PT-INR | 1.92 ± 0.31 | 2.15 ± 0.42 | ns |
| hs-CRP (mg/dl) | 0.18 ± 0.42 | 0.44 ± 0.65 | 0.0004 |
| BNP (mg/dl) | 97.1 ± 139.1 | 291.2 ± 288.8 | <0.0001 |
| CHADS ₂ score | 1.1 ± 1.1 | 2.2 ± 1.3 | <0.0001 |
| Left ventricular ejection fraction (%) | 64 ± 10 | 51 ± 18 | <0.0001 |
| Left ventricular end-diastolic volume (ml) | 99 ± 32 | 129 ± 68 | <0.0001 |
| Left atrial volume (ml) | 61 ± 26 | 99 ± 45 | <0.0001 |
| Degree of spontaneous echo contrast | 0.6 ± 1.0 | 2.1 ± 1.1 | <0.0001 |
| LAA emptying velocity (cm/s) | 46 ± 21 | 28 ± 17 | <0.0001 |
| LAA orifice area (cm ²) | 4.4 ± 3.1 | 6.3 ± 3.0 | 0.0006 |
| LAA depth (mm) | 34 ± 11 | 42 ± 12 | <0.0001 |
| LAA volume (ml) | 7.6 ± 7.1 | 12.1±5.8 | 0.0003 |
| Number of LAA lobes | 2.5 ± 0.8 | 3.4 ± 0.8 | <0.0001 |

Data are expressed as mean ± SD or as number (percentage).

AF = atrial fibrillation; BNP = B-type natriuretic peptide; CHADS₂ = Congestive heart failure, Hypertension Age > 75, Diabetes mellitus and prior Stroke or transient ischemic attack; LA = left atrium, LAA = left atrial appendage; PT-INR = prothrombin time/international normalized ratio.

Table 3 Univariate and Multivariate Analysis for Presence of LAA Thrombus

| Variable | Univariate | | Multivariate | |
|--|---------------------|---------|---------------------|---------|
| | OR (95% CI) | p Value | OR (95% CI) | p Value |
| AF type (Non-paroxysmal AF) | 4.785 (2.26-10.10) | <0.0001 | | ns |
| CHADS ₂ score | 1.915 (1.486-2.467) | <0.0001 | 1.752 (1.237-2.483) | 0.0016 |
| Degree of spontaneous echo contrast | 3.128 (2.262-4.326) | <0.0001 | 1.783 (1.102-2.740) | 0.0174 |
| Left ventricular ejection fraction (%) | 0.935 (0.914-0.956) | <0.0001 | 0.962 (0.934-0.992) | 0.0122 |
| LA volume (ml) | 1.031 (1.021-1.041) | <0.0001 | 1.018 (1.003-1.032) | 0.016 |
| LAA emptying velocity (cm/s) | 0.947 (0.925-0.970) | <0.0001 | | ns |
| LAA volume (ml) | 1.038 (1.007-1.070) | 0.0152 | | ns |
| Number of LAA lobes | 3.318 (2.179-5.052) | <0.0001 | 2.469 (1.495-4.078) | 0.0004 |

CI = confidence interval; OR = odds ratio. Other abbreviations as in Table 2.

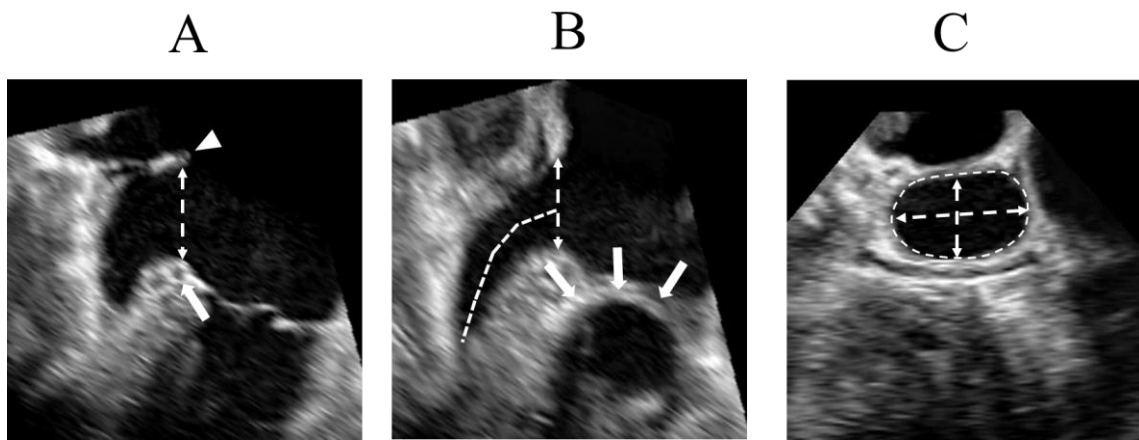
Table 4 Clinical Characteristics and Echocardiographic Measurements in Patients Who Maintained Sinus Rhythm After radiofrequency catheter ablation

| Variable | Baseline | After RFCA | p Value |
|--|-------------|-------------|---------|
| Men/Women | 36/10 | - | |
| Age (years) | 62 ± 9 | - | |
| BNP (mg/dl) | 124 ± 135 | 44 ± 52 | 0.0002 |
| hs-CRP (mg/dl) | 0.13 ± 0.14 | 0.09 ± 0.10 | 0.04 |
| Left ventricular ejection fraction (%) | 65 ± 10 | 69 ± 8 | 0.002 |
| Left ventricular end-diastolic volume (ml) | 103 ± 33 | 104 ± 27 | ns |
| Left ventricular end-systolic volume (ml) | 37 ± 20 | 33 ± 12 | 0.03 |
| E | 78 ± 20 | 72 ± 20 | ns |
| E' | 9.5 ± 2.6 | 13 ± 9 | 0.001 |
| E/E' | 8.6 ± 2.9 | 8.3 ± 3.3 | ns |
| Left atrial volume (ml) | 73 ± 25 | 63 ± 24 | 0.0001 |
| LAA emptying velocity (cm/s) | 38 ± 19 | 44 ± 19 | 0.02 |
| LAA filling velocity (cm/s) | 43 ± 22 | 46 ± 18 | ns |
| LAA orifice area (cm ²) | 4.4 ± 1.4 | 4.0 ± 1.2 | 0.003 |
| LAA depth (mm) | 37 ± 8 | 36 ± 7 | 0.002 |
| LAA volume (ml) | 7.4 ± 2.9 | 6.7 ± 2.6 | 0.0009 |
| Number of LAA lobes | 2.6 ± 0.7 | 2.6 ± 0.7 | ns |
| Degree of spontaneous echo contrast | 1.3 ± 1.2 | 0.70 ± 0.9 | <0.0001 |

Data are expressed as mean ± SD or as number (percentage).

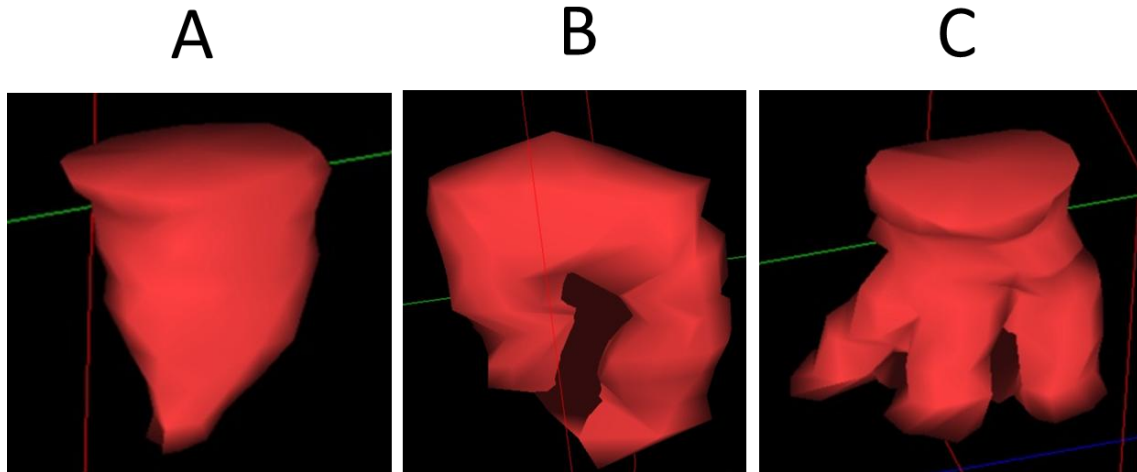
RFCA = radiofrequency catheter ablation, LAA = left atrial appendage.

Figure 1 Determination of the Left Atrial Appendage Orifice



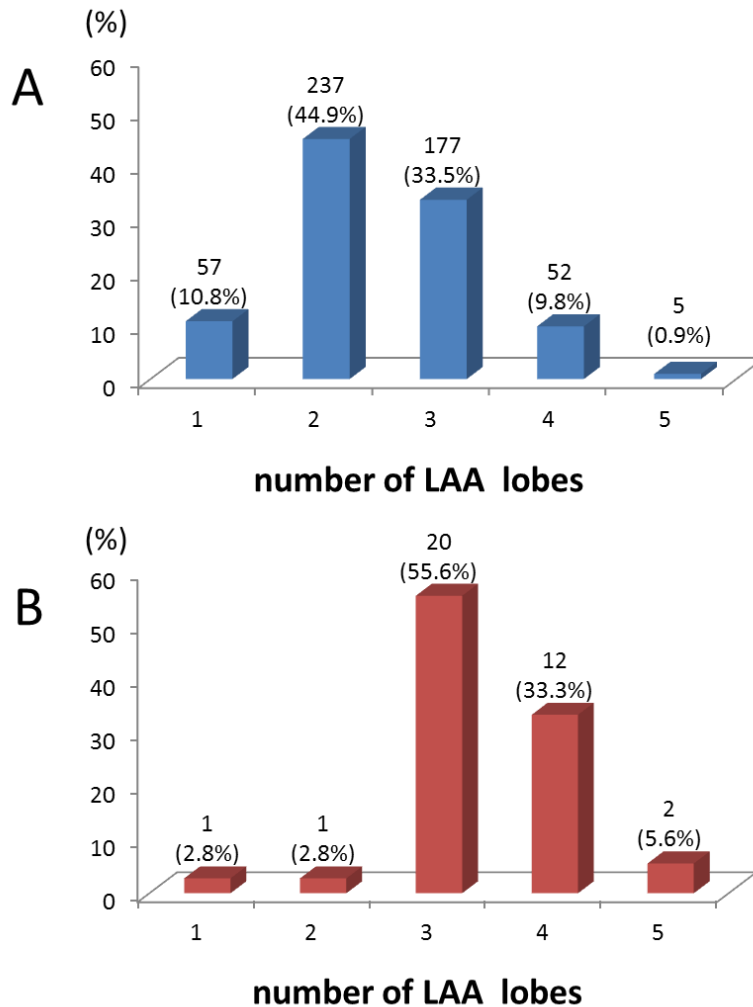
(A) Left atrial appendage (LAA) long-axis view at the level including the mitral valve annulus, left coronary artery (white arrow), and lateral ridge of the left superior pulmonary vein (white arrowhead). (B) LAA long-axis view at the level including the aortic valve annulus (white arrows). The dashed line with double-headed white arrows in both (A) and (B) corresponds to the line to determine the orifice of the LAA as shown in (C). In (B), the dotted line shows LAA depth. (C) LAA orifice area and long and short diameters.

**Figure 2 Representative Reconstructed 3D Images of the Left Atrial
Appendage**



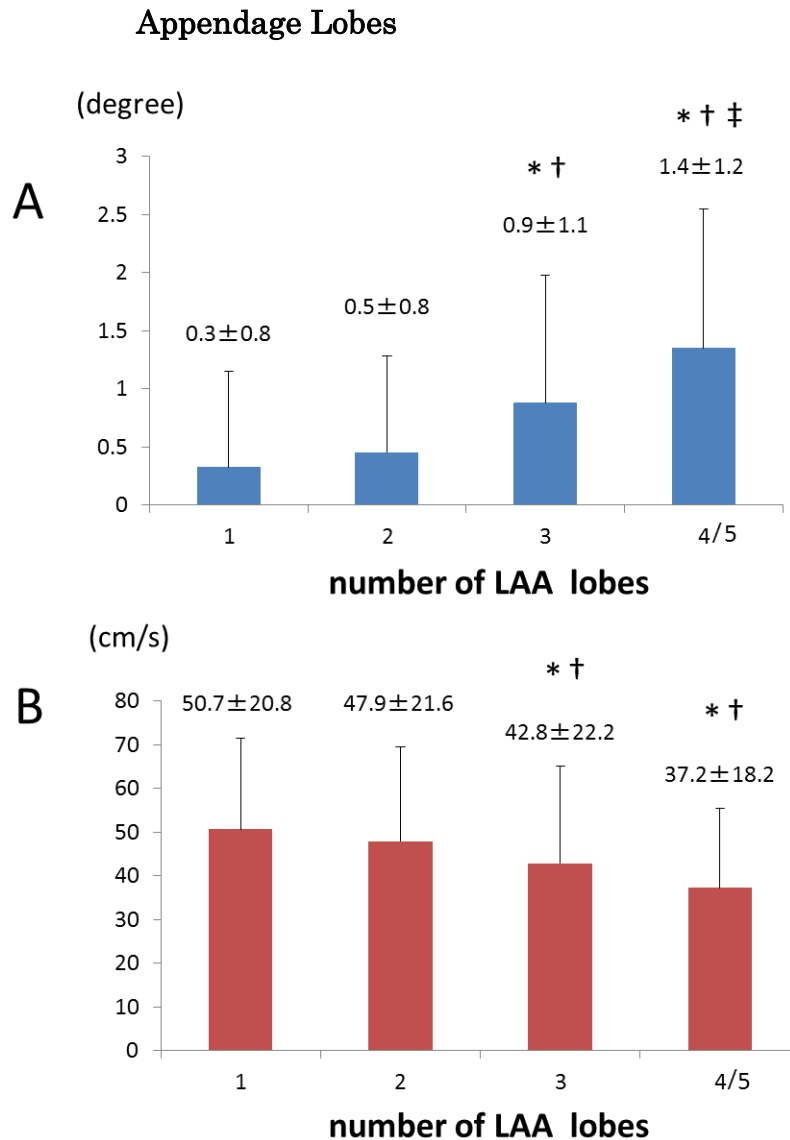
The reconstructed 3D image is of a left atrial appendage (LAA) with single lobe in panel A, an LAA with 2 lobes in panel B, and an LAA with 3 lobes in panel C. The green line indicates the coronal section line for ultrasonic beam direction, and the red line indicates the section line for a sagittal section.

Figure 3 Prevalence of Number of Left Atrial Appendage Lobes Between Patients With and Without Thrombus



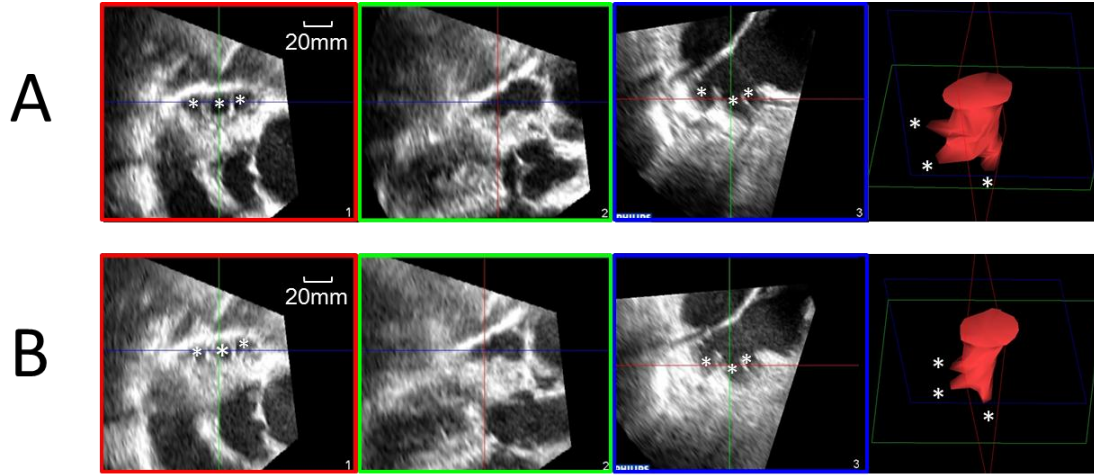
The graphs show the difference in the prevalence of number of left atrial appendage (LAA) lobes between patients without LAA thrombus (A) and with LAA thrombus (B). Most patients in the group without LAA thrombus (A) had 2 LAA lobes, whereas most patients in the group with LAA thrombus had 3 or more lobes.

Figure 4 Degree of Blood Stasis According to Number of Left Atrial



Panel A shows comparisons of the degree of spontaneous echo contrast (SEC) according to numbers of left atrial appendage (LAA) lobes. Panel B shows comparisons of LAA emptying velocity. *p < 0.05 vs. 1 lobe group; †p < 0.05 vs. 2 lobes group; ‡p < 0.05 vs. 3 lobes group

Figure 5 Representative Case of Left Atrial Appendage Remodeling After Catheter Ablation



The upper panel (A) shows baseline left atrial appendage (LAA) images and the lower panel (B) shows the corresponding images after catheter ablation.

The image in the red frame shows a short-axis view of the apex of the LAA lobe, that in the blue frame shows an LAA long-axis view (sagittal plane), and that in the green frame shows an LAA long-axis view (horizontal plane).

The rightmost image shows a 3D LAA image. The green line in the 3D LAA image indicates the horizontal section line for ultrasonic beam direction, the red line indicates a coronal section, and the blue line indicates a sagittal section. The LAA was reduced in size after catheter ablation (LAA volume, 17.8 ml to 10.3 ml; length of LAA neck, 23 mm to 14 mm), while the number of lobes (*) and fundamental morphology were maintained.

【謝辞】

本研究を進めるにあたり御指導を頂いた卒業論文指導教員の疾患制御医学専攻
循環器内科学 青沼和隆 教授に感謝致します。

また、論文の執筆にあたって親身に御指導いただきました疾患制御医学専攻
循環器内科学 瀬尾由広 准教授 並びに石津智子 講師に感謝致します。